

Lack of Effect of Coenzyme Q on Left Ventricular Function in Patients With Congestive Heart Failure

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- OBJECTIVES** This study evaluated the effects of oral therapy with coenzyme Q on echocardiographic and hemodynamic indexes of left ventricular function and on quality of life in patients with chronic left ventricular dysfunction.
- BACKGROUND** Coenzyme Q is a coenzyme for oxidative phosphorylation and an antioxidant and free radical scavenger. It has been claimed to improve symptoms, quality of life, left ventricular ejection fraction and prognosis in patients with cardiac failure.
- METHODS** Thirty patients with ischemic or idiopathic dilated cardiomyopathy and chronic left ventricular dysfunction (ejection fraction $26 \pm 6\%$) were randomized to a double-blind crossover trial of oral coenzyme Q versus placebo, each for 3 months. Right heart pressures, cardiac output and echocardiographic left ventricular volumes were measured at baseline and after each treatment phase, and quality of life was assessed using the Minnesota "Living With Heart Failure" questionnaire. It was calculated that to demonstrate an increase in left ventricular ejection fraction from 25% to 30% with a standard deviation of 5% using 95% confidence intervals with a power of 80% we would require 17 patients.
- RESULTS** Twenty-seven completed both treatment phases. There was no significant difference in left ventricular ejection fraction, cardiac volumes or hemodynamic and quality of life indices after treatment with coenzyme Q or placebo, although plasma coenzyme Q levels increased from $903 \pm 345 \text{ nmol/l}^{-1}$ to $2,029 \pm 856 \text{ nmol/l}^{-1}$.
- CONCLUSIONS** In patients with left ventricular dysfunction, treatment for three months with oral coenzyme Q failed to improve resting left ventricular systolic function or quality of life despite an increase in plasma levels of coenzyme Q to more than twice basal values. (J Am Coll Cardiol 1999;33:1549-52) © 1999 by the American College of Cardiology

Chronic heart failure is associated with significant morbidity and mortality. It has been speculated that defective myocyte energy production might be improved with mitochondrial enzyme supplementation, therefore improving contractility and clinical outcome.

Coenzyme Q (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone) was first isolated from beef heart in 1957 (1). It is a vitamin-like fat-soluble quinone found in high concentrations in the mitochondria of heart, liver and kidney (2), where it is involved in electron and proton transfer during oxidative phosphorylation (3). It is also an

antioxidant and free radical scavenger with membrane-stabilizing properties (4,5). It has been postulated that its depletion, which has been demonstrated in myocardial biopsies (6,7), may contribute to heart failure (8), and that it may be useful for treating a variety of conditions (9) including angina pectoris, diastolic dysfunction and cardiac failure. Several studies have claimed improvement in symptoms, quality of life, left ventricular ejection fraction and prognosis of patients with cardiac failure after oral coenzyme Q (10-12). We believe that these lack credibility because of small sample sizes, lack of controls and blinded randomization and the use of inaccurate or outdated methods to assess ventricular function.

We report the results of a placebo-controlled double-blind randomized crossover trial of coenzyme Q on resting left ventricular function in patients with heart failure stabilized on conventional vasodilator therapy.

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
D	=	dichloromethane
H	=	hexane

METHODS

Thirty patients, who were recruited from our heart failure and transplant unit, had chronic heart failure (duration 41 ± 35 months) and left ventricular dysfunction (ejection fraction $<35\%$ on echocardiography) for at least three months. They were clinically stable on maximum tolerated doses of angiotensin-converting enzyme (ACE) inhibitor therapy. Twenty-four were taking digoxin, 28 frusemide and 25 hydralazine and/or nitrates.

They were between 18 and 75 years of age with ischemic or idiopathic dilated cardiomyopathy. They were excluded if they had obstructive valvular heart disease, renal (serum creatinine >0.18 mmol/liter⁻¹) or hepatic (serum aspartate or alanine aminotransaminase $>$ upper limit of normal) impairment, a history of alcohol or drug abuse or an inadequate echocardiographic study, or if they were pregnant.

After informed consent and baseline echocardiography, patients were randomized to blinded treatment with coenzyme Q (33 mg t.d.s.) or identical placebo therapy. After 12 weeks there followed a washout period of 1 week before they were crossed to the alternate treatment arm for a further 12 weeks. Other therapy was altered only if indicated clinically. Transthoracic echocardiograms were repeated after each treatment phase and reviewed by four experienced sonographers blinded to the treatment protocol. Left ventricular end-diastolic and end-systolic volumes were measured and ejection fraction calculated using Simpson's biplane method (13).

To assess the reproducibility and interobserver variability of echocardiographic measurement, two experienced echocardiographers who were blinded to clinical condition independently assessed left ventricular end-diastolic and end-systolic volume and ejection fraction in 15 unselected patients whose left ventricular function varied from normal to severely depressed. There was a strong linear correlation between the observers ($r = 0.94$, $p < 0.001$). There was a small systematic difference in volume assessment ($<10\%$) and ejection fraction (12%). Bland and Altman analysis (14) did not demonstrate exaggeration of error at either end of the volume or ejection fraction spectrum.

Right heart catheterization was performed with a balloon flotation (Swan-Ganz) catheter at baseline and at the end of each treatment phase to measure right heart and mean pulmonary capillary wedge pressures and cardiac output using the thermodilution technique (15). Medications were not withheld.

Quality of life was assessed using the Minnesota "Living With Heart Failure" questionnaire (16) and routine biochemistry, liver function tests and blood count examination were performed at baseline and after each treatment phase. Patients were reviewed each month.

Plasma coenzyme Q determination. Plasma coenzyme Q levels were measured at baseline and at the end of each treatment phase using high performance liquid chromatography (17-19) with a reverse-phase C-18 column (20 to 25 cm, 5- μ m particle size). The mobile phase was a 15:18 hexane:methanol solution which was delivered at 2 ml/min⁻¹, with the samples measured at a wavelength of 280 nm. Blood was collected into lithium heparin tubes. A coenzyme Q standard in phosphate buffer (0.05 mol/l, pH 7.4) was used at a concentration of 1181 nmol/liter⁻¹. Coenzyme Q₉ in ethanol was used as the internal standard. This was added to both the standard coenzyme Q and plasma tubes before extraction. Coenzyme Q standards and plasma samples (500 μ l) were extracted with 2 ml of methanol and 9 ml of hexane. The tubes were shaken vigorously horizontally for 5 min and centrifuged for 10 min. The top hexane layer was evaporated under nitrogen in a 40°C water bath. The samples were then reconstituted into 500 μ l of a 1:3 hexane:dichloromethane (H:D) solution and applied to silica Sep-Pak (Waters Corp., Milford, Massachusetts) columns (690 mg) which had been washed with 12.5 ml of the H:D solution. The columns were then washed with 3.5 ml of the H:D solution, with coenzymes Q₉ and Q₁₀ being retained on the column. The coenzyme Q fraction was further eluted with 5 ml of the H:D solution, evaporated under nitrogen and reconstituted into 120 μ l of ethanol for measurement by high performance liquid chromatography. Eleven control subjects (each with cholesterol levels within the reference range) were assayed, giving a mean of 798 ± 205 nmol/liter⁻¹.

Statistical methods. We compared echocardiographic and hemodynamic data during treatment with coenzyme Q or placebo with multivariate analysis of variance. We calculated that to demonstrate an increase in left ventricular ejection fraction from 25% to 30% with a standard deviation of 5% using 95% confidence intervals with a power of 80% we would require 17 patients. Quality of life scores with coenzyme Q or placebo were compared with Friedman two-way analysis of variance.

RESULTS

Thirty patients were randomized between April 1994 and October 1995 (Table 1). All were stable clinically and on ACE inhibitor therapy. Three did not complete the trial (one died of heart failure while taking placebo and two underwent cardiac transplantation because of persisting symptoms). Echocardiographic and hemodynamic data are shown in Table 2. Values on active treatment or differences

Table 1. Patient Demographics and Clinical Details

Number randomized	30
Mean age (yr)	55 ± 11
Male	26 (87%)
Duration of heart failure (mo)	41 ± 35
Dilated cardiomyopathy	23 (77%)
Ischemic cardiomyopathy	7 (23%)

between baseline and active treatment did not differ significantly from those on placebo medication (Fig. 1).

Plasma levels of coenzyme Q at baseline and after each treatment phase were available on 20 patients. After active treatment these increased from 903 ± 345 nmol/liter⁻¹ (baseline) to $2,029 \pm 856$ nmol/liter⁻¹.

There was no difference in well-being or functional capacity with coenzyme Q or placebo as assessed with the Minnesota “Living With Heart Failure” questionnaire (16) ($p = 0.22$). The mean sum of all scores at baseline was 29.4 ± 16.6 (median 23), on coenzyme Q 26.7 ± 17.9 (median 22) and on placebo 26.5 ± 18.7 (median 22).

Coenzyme Q was well tolerated and its use was associated with no adverse effects, deterioration in renal or hepatic function or alteration in hematologic parameters.

DISCUSSION

Folkers et al. suggested that coenzyme Q might be helpful in those with cardiac failure because of its deficiency in the myocardium and plasma of such patients (8). We studied patients with chronic left ventricular dysfunction to determine if a dose of 100 mg daily would improve resting left ventricular systolic function. All had chronic heart muscle dysfunction, were clinically stable and were receiving ACE inhibitor therapy in doses which were considered optimal or were limited by postural hypotension or renal dysfunction. Changes in treatment during the trial were avoided as far as possible.

Coenzyme Q for 3 months produced no demonstrable improvement in resting left ventricular ejection fraction (Fig. 2), volumes (Table 2, Fig. 1) or quality of life scores compared with placebo. The pathophysiology of heart failure may be too complex to be explained simply by the depletion of myocardial energy stores and therefore likely to be reversed by coenzyme Q.

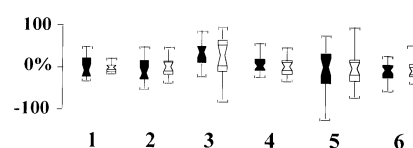


Figure 1. Box-and-whisker plots showing changes in values (delta %, y axis) from baseline for (1) left ventricular systolic volumes, (2) diastolic volumes, (3) ejection fraction, (4) cardiac index, (5) pulmonary artery wedge pressure and (6) systemic vascular resistance during treatment with coenzyme Q (dark shading) and placebo (light shading). The height of the boxes shows the interquartile distance (the difference between the third quartile of the data and the first quartile). The notch is shown at the median of the data, and the whiskers extend to the extreme values of the data or 1.5 times the interquartile distance from the center, whichever is less.

Study limitations. The dose and the duration of therapy were similar to other studies and were sufficient to achieve a greater than twofold increase in plasma levels of coenzyme Q (20–22). Nevertheless, as we did not perform myocardial biopsies we cannot be sure that myocardial stores were replenished nor can we comment on whether beginning coenzyme Q therapy earlier in the natural history of the disease might have improved left ventricular function.

Although there is a degree of intraobserver variability in echocardiographic measurements of cardiac volumes, this was minimized by limiting interpretation to a few experienced echocardiographers blinded to the treatment. All studies were reviewed independently to establish uniformity in reporting. We were concerned with the difficulty of proving the null hypothesis but calculated that the study was adequately powered to demonstrate an increase in left ventricular ejection fraction by 5%.

Indexes of pump function such as left ventricular ejection fraction and end-systolic volume are sensitive to loading conditions. Although changes in doses of vasodilator therapy during the trial were unavoidable in some patients, there were no significant changes in pulmonary artery wedge pressure or systemic vascular resistance in the treatment groups.

Conclusions. In patients with chronic left ventricular dysfunction secondary to ischemic or idiopathic cardiomyopathy taking maximal conventional therapy, treatment for 3 months with coenzyme Q failed to improve resting left

Table 2. Echocardiographic and Hemodynamic Data

	Baseline	Coenzyme Q	Placebo	p <*
Left ventricular diastolic volume (ml)	220 ± 72	209 ± 75	220 ± 68	0.16
Left ventricular systolic volume (ml)	167 ± 54	149 ± 61	155 ± 58	0.26
Ejection fraction (%)	26 ± 6	31 ± 9	31 ± 9	0.98
Cardiac index	2.7 ± 0.7	2.9 ± 0.7	2.9 ± 0.7	0.46
Pulmonary wedge pressure (mm Hg)	16 ± 6	16 ± 7	16 ± 7	0.40
Systemic vascular resistance (U)	16 ± 4	15 ± 4	15 ± 5	0.24

*Multivariate analysis of variance coenzyme Q versus placebo, effect–order of treatment.

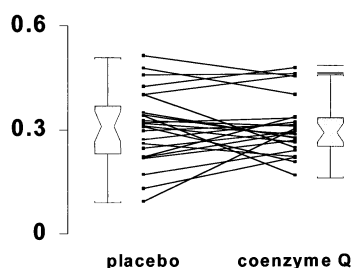


Figure 2. Box-and-whisker plots of left ventricular ejection fraction (y axis) during treatment with placebo and coenzyme Q, with line plots showing paired values for each subject.

ventricular ejection fraction. This was despite an increase in plasma levels of coenzyme Q to more than twice basal values.

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